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MARK K JOHNSON
P O BOX 510644
NEW BERLIN, WI 531310644

EXAMINER

GOLDBERG, JEANINE ANNE

ART UNIT PAPER NUMBER

1634

DATE MAILED: 03/06/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

CINE

Office Action Summary**Application No.**

09/109,119

Applicant(s)

BOLDT ET AL.

Examiner

Jeanine A Goldberg

Art Unit

1655

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 January 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-16 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-16 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other: _____

DETAILED ACTION

1. This action is in response to the papers filed January 29, 2002.
2. The request filed on January 29, 2002 for a Request for Continuing Examination (RCE) is acceptable and a REE has been established. An action on the RCE follows.
3. Currently, claims 1-16 are pending. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.
4. Any objections and rejections not reiterated below are hereby withdrawn.
5. This action contains new grounds of rejection necessitated by amendment.
6. The amendment to the claims filed on January 29, 2002 does not comply with the requirements of 37 CFR 1.121(c). Amendments to the claims filed after March 1, 2001 must comply with 37 CFR 1.121(c) which states:

(c) Claims.

(1) Amendment by rewriting, directions to cancel or add: Amendments to a claim must be made by rewriting such claim with all changes (e.g., additions, deletions, modifications) included. The rewriting of a claim (with the same number) will be construed as directing the cancellation of the previous version of that claim. A claim may also be canceled by an instruction.

(i) A rewritten or newly added claim must be in clean form, that is, without markings to indicate the changes that have been made. A parenthetical expression should follow the claim number indicating the status of the claim as amended or newly added (e.g., "amended," "twice amended," or "new").

(ii) If a claim is amended by rewriting such claim with the same number, the amendment must be accompanied by another version of the rewritten claim, on one or more pages separate from the amendment, marked up to show all the changes relative to the previous version of that claim. A parenthetical expression should follow the claim number indicating the status of the claim, e.g., "amended," "twice amended," etc. The parenthetical expression "amended," "twice amended," etc. should be the same for both the clean version of the claim under paragraph (c)(1)(i) of this section and the marked up version under this paragraph. The changes may be shown by brackets (for deleted matter) or underlining (for added matter), or by any equivalent marking system. A marked up version does not have to be supplied for an added claim or a canceled claim as it is sufficient to state that a particular claim has been added, or canceled.

(2) A claim canceled by amendment (deleted in its entirety) may be reinstated only by a subsequent amendment presenting the claim as a new claim with a new claim number.

It is noted that applicants have bracketed out the entire previous, claim and underlined the entire new claim. This amendment does not illustrate the portions of the claim which have been changed and intended by the marked up copy of the claims. In the

future, the examiner requests that amendments to the claims clearly illustrate the changes.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A2) Claims 1-16 are rejected because it is unclear what is meant by "determine if at least one base is present". The claim appears to require that hybridization between the primer and the genomic DNA will only occur if "the base is present". However, the primer, even in the event that the last nucleotide is mismatched, it appears from the specification that hybridization will occur. Only when the primer is extended, will a difference between a mismatch and a complementary nucleotide allow discrimination. In step b "wherein the primer 3' nucleotide will hybridize and extend along the genomic DNA if the base is present", does not clearly illustrate the summary of the invention found on page 7 of the specification. The 3' base of the primer is likely to be present, however the assay will determine the nucleotide present at the position. As written the amplification would only fail in the instance in which the target genomic DNA is one nucleotide shorter than the primer on the 3' end. Amplification will occur in all other cases, since a base is present. Clarification is requested.

B2) In step (d) "the targeted sequence" lacks antecedent basis. Furthermore, it is unclear whether the primer is amplified or whether the genomic DNA is amplified. Based upon the teachings in the specification, the primer is amplified as opposed to the targeted sequence.

C2) Claim 2 is indefinite because it is unclear how Claim 2 further limits claim 1. Claim 1 requires in step (e) capturing amplified sequence to a solid support wherein the solid support contains probes that hybridize to amplified product having the base. Claim 2 requires that the capturing amplified polynucleotide strands comprises hybridizing the strands to a probe. The limitations of Claim 2 appear to be in step (e).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1, 2, 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Newton et al (US Pat. 5,525,494, June 1996).

Newton et al. (herein referred to as Newton) teaches a method for testing genomic DNA to determine if at least one base is present by making a solution comprising genomic DNA, adding a primer which hybridizes to a targeted section of the genomic DNA, wherein the primer 3' nucleotide will hybridize and extend along the

genomic DNA if the base is present, mixing DNA polymerase into the solution, amplifying the genomic DNA if the base at the 3' end of the primer hybridizes, capturing the amplified polynucleotide strand, and detecting the amplified polynucleotide.

Specifically, Newton teaches ARMS uses primers that allow amplification in an allele specific manner such that amplification is inhibited when the 3' terminal base of the primer is mismatched (col. 4, lines 45-50). ARMS may be used and captured on a single solid phase (col. 4, lines 55-60). Newton teaches that both ARMS signal primers are labeled with a different fluorophore such as rhodamine. The two colors, namely red and green and their combination of yellow, allow detection of all normal and variant heterozygotes and homozygotes. Newton teaches capturing the polynucleotides on a solid support which contains probes sequences to hybridize to amplified products. Two different solids phases are described by Newton such that one of the phases is specific to the variant nucleic acid and the other is specific to the normal nucleic acid (col. 4-5)(limitations of Claim 1e and 13e). Newton teaches that the capture on solid phases is particularly useful in respect of dipstick type assay formats (col. 5, lines 14-15). As provided in Example 5, the specific capture and detection of amplification products based on the S locus of the alpha-1 antitrypsin gene (col. 24, lines 56-60).

ARMS analysis is performed using DNA, ARMS primer, and Taq polymerase (col. 27, lines 15-25)(limitations of Claims 1 and 13). Specifically, DNA, oligonucleotide 11 (specific for the normal allele) were added to Tube S normal (limitations of Claim 1 and 13 a and b)(col 27, line 20). A second tube comprising the same reagents, namely DNA and oligonucleotide 12 (specific for the mutant allele) was mixed (limitation of

Claim 1 and 13 a and b)(col 27, lines 22). Taq polymerase was added to the tubes (limitations of Claim 1 and 13 c)(col 27, line 27). The nucleic acids within the tubes were subjected to extension step (amplification) (limitations of Claim 1 and 13 d)(col 27, lines 32). For solid phase capture and detection of ARMS products, 20 ul of PCR product from both the S normal primer tube and the S variant primer tube were added to wells and allowed to hybridize for an hour (col 28, lines 11-18). 200 ul of color development solution was added to each well and the wells were scanned to allow detection (limitations of Claim 1 and 13 f)(col 28, lines 29-35). The color allows detection and clear diagnosis (col 28, lines 39-40) (limitations of Claim 6, 8, 9, 10). Newton teaches there is no significant non-specific binding, ie there is no color in the control wells A3 and B3. Oligonucleotides are immobilized to microtitre dishes (col. 26, lines 55-65)(limitations of Claim 7).

Response to Arguments

The response filed January 29, 2002 traverses the rejection. The response asserts that Newton does not teach "capturing amplified polynucleotide stands to a solid support. Newton's primer sequences hybridize to probes attached to the solid support." (page 2 of response filed January 29, 2002). This argument has been thoroughly reviewed but is not convincing because as admitted by the response Newton does teach capturing amplified polynucleotide strands to a solid support. Example 5 is directed to this embodiment. Example 5 is an example for the specific capture and detection of amplification products. Solid phase capture and detection of ARMS products is described in column 28. PCR products from the S normal primer tube and

the PCR product from the S variant primer tube were added to different well within the microtiter plate and allowed to hybridize.

The response asserts that when primer sequences are complementary to and hybridize to the probe, a severe competition problem occurs since there will be many more non-amplified primers available for hybridization than primers that have initiated an amplified product (page 2 or response filed January 29, 2002). The response asserts that Newton's non-amplified primers create detection problems. This argument has been thoroughly reviewed but is not convincing because the instant method steps of the claims are taught by Newton. Newton teaches there is no significant non-specific binding, i.e. there is no color in the control wells A3 and B3.

Thus for the reasons above and those already of record, the rejection is maintained.

9. Claims 1, 2, 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Ugozzoli et al. (GATA, Vol. 9, No. 4, pages 107-112, 1992).

Ugozzoli et al. (herein referred to as Ugozzoli) teaches a method of detection of specific alleles by using Allele-specific primer extension followed by capture on solid support. Ugozzoli teaches a method of making a solution comprising genomic DNA (page 108, col 2) (b) adding a primer that hybridizes to a targeted sequence of the genomic DNA (page 109, col 1) (c) mixing a DNA polymerase (page 109, col 1) (d) amplifying the targeted sequence of the genomic DNA if the base is present (page 109,

col 1) (e) capturing amplified sequence to a solid support and (f) detecting (page 109, col 1-2). As seen in Figure 1, the method steps are clearly outlined.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

10. Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Newton et al (US Pat. 5,525,494, June 1996) in view of Monforte et al. (US Pat. 5,700,642, December 1997).

Newton et al. (herein referred to as Newton) teaches a method for testing genomic DNA to determine if at least one base is present by making a solution comprising genomic DNA, adding a primer which hybridizes to a targeted section of the genomic DNA, wherein the primer 3' nucleotide will hybridize and extend along the genomic DNA if the base is present, mixing DNA polymerase into the solution, amplifying the genomic DNA if the base at the 3' end of the primer hybridizes, capturing the amplified polynucleotide strand, and detecting the amplified polynucleotide. Specifically, Newton teaches ARMS uses primers that allow amplification in an allele specific manner such that amplification is inhibited when the 3' terminal base of the primer is mismatched (col. 4, lines 45-50). ARMS may be used and captured on a

single solid phase (col. 4, lines 55-60). Newton teaches that both ARMS signal primers are labeled with a different fluorophore such as rhodamine. The two colors, namely red and green and their combination of yellow, allow detection of all normal and variant heterozygotes and homozygotes. Newton teaches capturing the polynucleotides on a solid support which contains probes sequences to hybridize to amplified products. Two different solids phases are described by Newton such that one of the phases is specific to the variant nucleic acid and the other is specific to the normal nucleic acid (col. 4-5)(limitations of Claim 1e and 13e). Newton teaches that the capture on solid phases is particularly useful in respect of dipstick type assay formats (col. 5, lines 14-15). As provided in Example 5, the specific capture and detection of amplification products based on the S locus of the alpha-1 antitrypsin gene (col. 24, lines 56-60). ARMS analysis is performed using DNA, ARMS primer, and Taq polymerase (col. 27, lines 15-25)(limitations of Claims 1 and 13). Specifically, DNA, oligonucleotide 11 (specific for the normal allele) were added to Tube S normal (limitations of Claim 1 and 13 a and b)(col 27, line 20). A second tube comprising the same reagents, namely DNA and oligonucleotide 12 (specific for the mutant allele) was mixed (limitation of Claim 1 and 13 a and b)(col 27, lines 22). Taq polymerase was added to the tubes (limitations of Claim 1 and 13 c)(col 27, line 27). The nucleic acids within the tubes were subjected to extension step (amplification) (limitations of Claim 1 and 13 d)(col 27, lines 32). For solid phase capture and detection of ARMS products, 20 ul of PCR product from both the S normal primer tube and the S variant primer tube were added to wells and allowed to hybridize for an hour (col 28, lines 11-18). 200 ul of color development solution was

added to each well and the wells were scanned to allow detection (limitations of Claim 1 and 13 f)(col 28, lines 29-35). The color allows detection and clear diagnosis (col 28, lines 39-40) (limitations of Claim 6, 8, 9, 10). Newton teaches there is no significant non-specific binding, ie there is no color in the control wells A3 and B3.

Oligonucleotides are immobilized to microtitre dishes (col. 26, lines 55-65)(limitations of Claim 7).

Newton does not specifically teaches denaturing the amplified polynucleotides to form single-stranded polynucleotides prior to hybridization on a solid support.

However, Monforte teaches that primer extension products are routinely denatured from the target, using heat or chemical denaturant. Monforte also teaches "coupling of an oligonucleotide to a solid support may be carried out through a variety of immobilization attachment functional groups" (col. 17, lines 39-45). This includes biotinylated oligonucleotides which is immobilized by attachment to a streptavidin-coated support (col. 19, lines 54-66).

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Newton for ARMS primer extension on a solid support with the teachings of Monforte that denaturing the extension product is routine in the art prior to subsequent hybridization to a solid support. The skilled artisan would have been motivated to have denatured the primer extension product of Newton with either chemical or heat denaturation methods for the expected benefit of obtaining suitable nucleic acid for further hybridization analysis.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the solid support attachment method of Newton with the equivalent as taught by Monforte. The skilled artisan would have recognized by the extensive teachings of Monforte that oligonucleotides may be linked to solid supports using numerous means. The utilization of a streptavidin/biotin was one equivalent means for attaching oligonucleotides to a solid support.

Response to Arguments

The response filed January 29, 2002 traverses the rejection. The response asserts that Newton nor Monforte are not selective for amplified product. The response also argues that "applicants' process utilizes the sequence of amplified product for attachment, not primer sequence" (page 3 of response filed January 29, 2002). This argument has been reviewed but is not convincing because the claims require capturing amplified sequence to a solid support wherein the solid support contains probes that hybridize to amplified product having the base. The claims are not directed to using amplified product for attachment, not product sequence. The specification does not appear to support this interpretation asserted in the response. Example 5 of Newton is directed to this embodiment. Example 5 is an example for the specific capture and detection of amplification products. Solid phase capture and detection of ARMS products is described in column 28. PCR products from the S normal primer tube and the PCR product from the S variant primer tube were added to different well within the microtiter plate and allowed to hybridize. Newton teaches there is no significant non-specific binding, i.e. there is no color in the control wells A3 and B3.

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Thus for the reasons above and those already of record, the rejection is maintained.


Conclusion


11. No claims allowable over the art.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Enewold Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Thursday from 7:00AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jeanine Enewold Goldberg
February 26, 2002 


W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600